The effect of intrathecal Clonidine on post-operative analgesia in pregnant patients undergoing lower segment caesarean section

A study of 70 cases

Dissertation

Submitted in partial fulfillment of university regulations for the award of

M.D. DEGREE EXAMINATION

BRANCH X – ANAESTHESIOLOGY

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

MARCH 2010

CERTIFICATE

This is to certify that the Dissertation **"The effect of intrathecal clonidine on post-operative analgesia in pregnant patients undergoing lower segment caesarean section"** presented herein by **Dr. D. PALARAMAKRISHNAN** is an original work done in the Department of Anaesthesiology, Tirunelveli Medical College Hospital, Tirunelveli for the award of Degree of M.D. (Branch X) Anesthesiology under my guidance and supervision during the academic period of 2008-2010.

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DECLARATION

I, **DR. D. PALARAMAKRISHNAN** declare that the dissertation titled "**The effect of intrathecal clonidine on post-operative analgesia in pregnant patients undergoing lower segment caesarean section**" has been prepared by me.

This is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for the award of M.D. Degree, Branch X (ANAESTHESIOLOGY) degree Examination to be held in March 2010.

Place : Tirunelveli

Date :

DR.D.PALARAMAKRISHNAN

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CONTENTS

INTRODUCTION

"For all the happiness mankind can gain is not in pleasure, but in rest from pain"

John Dyrden

The relief of pain during surgery is the raison d'etre of anaesthesia. Pain is a fundamental biological phenomenon. The aim of anaesthesiology as a science is the removal of pain temporarily, started initially with pain relief for surgeries, and now extends to post operative pain relief, relief of chronic pain, and cancer pain.

Effective post operative analgesia reduces post operative morbidity, allows early ambulation and discharge. Post operative analgesia is achieved by various techniques using various drugs among which neuraxial blockade plays an important role.

The accidental entry of corning's needle in 1885, in to the subarachnoid space paved the way for the greatest leap into spinal anaesthesia. His words "Be the destiny of this observation, what it may, has seemed to me on the whole worth recording..," opened the prologue. The word spinal anaesthesia was coined by him.

History of Pain

An anesthesiologist has a role to relieve pain due to various causes including post operative pain.

Pain – The word derived from a Greek word “poine” which means penalty.

Pain is defined as an unpleasant sensory and emotional experience which is associated with actual tissue damage or potential of tissue damage or at least described in terms of such damage.

Aristotle – Described that the pain was an emotion emanating from the heart.

Galen – Correctly observed brain was required to manifest the pain and he also proposed that sensation is a property of nervous tissue.

The idea of specific neural pathways for painful sensations began with **CHARLES BELL** (1774-1842) and **FRANCOIS MAGENDIE** (1783-1855) who both demonstrated that dorsal roots of the spinal cord transmit sensory informations and the ventral root transmit the motor informations.

In 1948 Ahlquist proposed the designations of α and β receptors. Since then various subtypes of these two main classes have been characterized. Various theories regarding pain transmission including gate control theory (1965) by Melzack and Wall. Endogenous opioids are located at diverse sites in the pain pathway, including dorsal horn of influence rostral transmission of Pain. By using intrathecal or epidural injection, the nociceptive transmission at the 1st synaptic relay in the spinal cord may be manipulated.

The α_2 adrenergic mechanisms have been exploited for more than hundred years. Cocaine, the first spinal anesthetic primarily produces analgesia by its local anesthetic properties and also in which nor-adrenaline re-uptake, in part by increasing noradrenergic stimulation of α_2 receptors. Veterinarians have used α_2 agonists (Detomidine, Meditomidine)

for many years for regional analgesia, but experience with these agents in humans, dates back only slightly more than ten years.

In 1984 Tamsen, Gordh after testing neuro toxicity in animals and then injected a parental preparation of α_2 agonist Clonidine, epidurally in two patients with chronic pain. Since then the complete toxicologic assessment in animal studies has suggested that Clonidine is safe for intrathecal use.[1]

Physiology of pain

Pain is a complex phenomenon and includes both

- sensory – discriminative and
- motivational – affective components

Sensory –discriminative component:

This component depends upon the ascending projection of tracts like spinothalamic and trigeminothalamic tracts into the cerebral cortex. Thus they help to perceive the quality of pain that is pricking, burning quality etc. They also help to know the location of stimulus, intensity and duration of the stimulus.

Motivational - affective component:

It includes attention, arousal, somatic, autonomic reflexes, endocrine and emotional changes. These collectively contribute to the unpleasant nature of pain.

Pain receptors: (Nociceptors)

These are the free nerve endings present in the skin, muscles, joints, viscera, and in the vasculature. Theses receptors detects the noxious stimulus due to the chemical, thermal (heat, cold) and mechanical changes. In normal tissues they are inactive and are stimulated by a sufficient energy to overcome their resting threshold. Thus they prevent random signal propagation to central nervous system for interpretation of pain. This is so called screening function. The nociceptive neurons synapse in the dorsal horn of the spinal cord with both local interneurons and projection neurons that carry the nociceptive information to the higher centers present in the brainstem, thalamus. In contrast to the other sensory receptors **" the pain receptors do not adapt "** and this unique feature is protective and thus allows the individual to aware of continued tissue damage. After damage, pain is usually minimal and also the onset pain depends upon the rate of metabolism. e.g. ischemic injury of the skin usually produces pain with 20 to 30 minutes, but for the exercising muscles the pain occurs within 15 to 20 seconds. Certain specific types of nociceptors reacts only to the specific stimuli, but other nociceptors react to multiple stimuli for e.g. " C " nociceptors and A delta nociceptors reacts to heat or cold stimuli. Some Aβ receptors which are usually mechanoreceptors may have nociceptor like activity. Aβ mechanoreceptor sensory fibers can be recruited to transmit signals that will interpret as painful stimuli. But it occurs only when these receptors are in the environment of inflammation. The mechanical allodynia (painful sensation results from light touch) results from Aβ receptors recruitment.

Visceral receptors:

These are not designed solely as pain receptors because the internal organs are not frequently exposed to potentially damaging events. Many damaging events like cutting, burning, clamping the visceral organs do not produce pain but the ischemic injury, inflammation, dilation, spasm of hollow organ and stretching of the mesentery produces pain.

Neurobiology of pain

The experience of pain involves a series of complex physiologic processes which includes four components. They are

A) **Transduction:** is the process by which the noxious stimuli is converted in to an electrical impulse in sensory nerve endings.
B) **Transmission:** Is the process by which these electrical impulses are conducted to central nervous system through the connections in the dorsal horn of the spinal cord and thalamus with projections to the cingulated, insular and somatosensory cortexes.
C) **Modulation:** Is the process of altering the pain transmission that is both inhibitory and excitatory mechanisms present in the peripheral nervous system and central nervous system.
D) **Perception:** Is thought to occur at thalamus and the cortex is important for the discrimination of specific sensory experiences.

Pain may occur even in the absence of any of these above four steps. For example pain due to **trigeminal neuralgia occurs in the absence of transduction of chemical stimulus at nociceptor.**

Modulation may be absent if specific nervous system tracts are injured for example - phantom limb pain occurs in the absences of nociceptors.

Transduction:

When the resting thresholds of the sensory nerve endings are exceeded by mechanical, chemical or thermal changes, these mechanical or chemical changes or converted into an electrical action potential and is transmitted to the spinal cord. Nociceptors generates action potential that results in the perception of pain before tissue damage occurs (protective). A delta and “C” fibers undergo peripheral sensitization when they are exposed

to inflammatory mediators, so that their firing thresholds decrease, but their firing is increased with increased intensity and duration. But in majority of the cases when acute inflammation subsides, this process naturally resolves and peripheral sensitization decrease and the nociceptors returned to their original resting threshold. But in chronic pain they do not return to the original resting threshold which results in the persistent pain sensation and presents as allodynia or hyperalgesia.

Transmission:

Pain signals transmitted from the nociceptive receptors along the myelinated A δ fibers (which is responsible for rapid conduction and early response) and unmyelinated "C" fibers (which is responsible for slow conduction and delayed response). These fibers enter the spinal cord through dorsal nerve root and terminate on the cells in the dorsal horn.

Modulation:

Peripheral modulation*:*

Occurs by liberation or elimination of chemicals near the nociceptor. Tissue injury activates nociceptor in the periphery by releasing neurotransmitters like substance P, glutamate that directly activate nociceptors. Other mediators like bradykinin, prostaglandin further sensitizes and excites the receptors and also acts as mediators of inflammation. Ischemic injured cells, mast cells, plasma, platelets surrounding the receptors are the sources of these mediators. Drugs like NSAID by inhibiting the prostaglandin synthesis may influence the peripheral modulation, but Clonidine has no role at the periphery.

Spinal modulation*:*

It occurs due to actions of neurotransmitters at dorsal horn or from spinal reflexes which convey the efferent impulses back to the peripheral nociceptive field. Glutamate, aspartate, neuropeptide Y are the excitatory substances involved in the regulation of pain transmission. GABA, glycine, noradrenaline are inhibitory substances involved in the pain transmission. Clonidine has a role at dorsal horn of the spinal cord.

***Supraspinal modulation**:*

Includes endogenous narcotics and monoamine pathways which have cell bodies situated around the periaqueductal greymatter and these are the descending inhibitory pathways. They descend in to the dorsolateral fasciculus and synapse in the dorsal horn. Neurotransmitters act pre-synaptically on first order neuron and post-synaptically on second order neurons in the spinothalamic tract. Analgesia is produced by electrical stimulation of the peri-aqueductal gray matter. Neurotransmitters released from these projections hyperpolarize the A delta fibers and C fibers that serve to negate depolarizing currents that approach the terminal endplates and thus diminishing the release of neurotransmitters like suptance P. Hyperpolarization of nerves most likely occurs because of the opening of potassium ion channels and inhibition of calcium ion movement.

***Cognitive modulation**:*

This involves the patient's ability to relate a painful experience to another event, so that the pain experienced in pleasant environment is less intense than that experienced in the setting of depression. Another area of perception is attention which allows only fixed number of afferent impulses to the cortical centers, so that, if the patient concentrate on separate unrelated thing, it is possible to decrease the painful sensations (biofeedback or hypnosis).

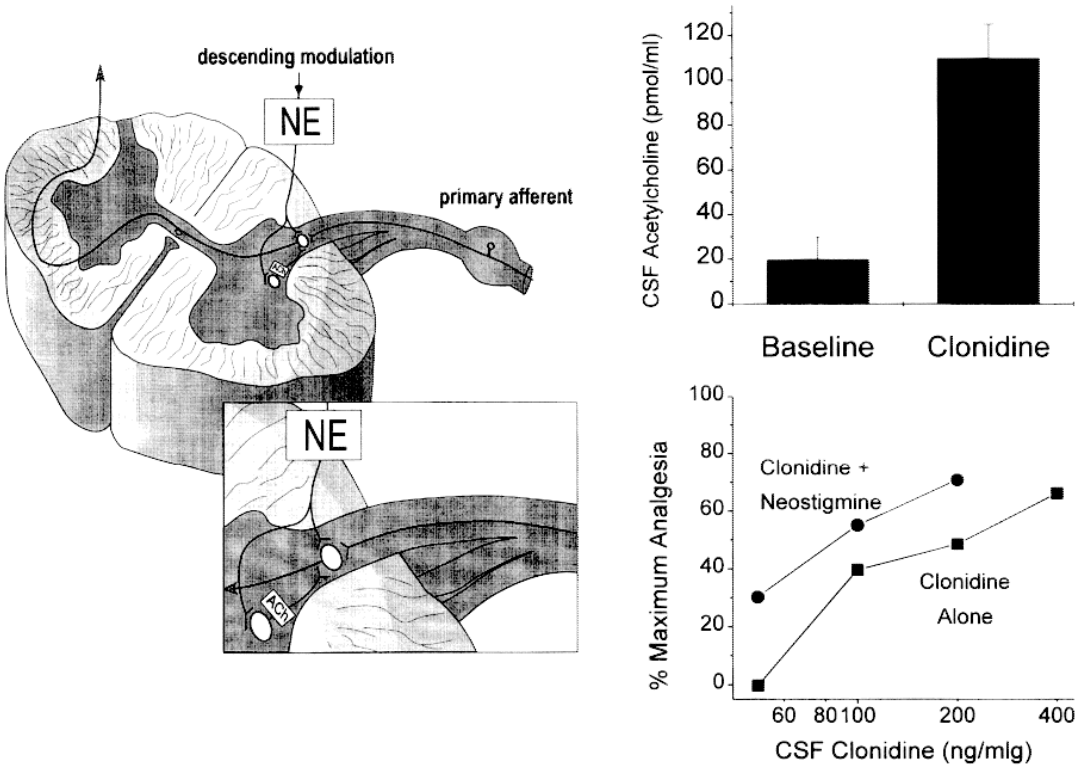
Dorsal horn and ascending nociceptive pathways

Primary afferent fibers with their cell bodies in the dorsal root ganglion which is connected second neuronal cell located in the dorsal horn. Afferent fibers from the peripheral receptors enters the spinal cord then ascend and descend several segments in the lissauer tract in the dorsal horn.

Dorsal horn of the spinal cord contains six laminae

Laminae I and II are the sites of termination of afferent C fibers and these two laminae collectively known as substantia gelatinosa which is important for integration and modulation of incoming nociceptive information.

Laminae V is the site which receives the input from both nociceptive and non-nociceptive neurons. Second order wide dynamic range neurons (W.D.R) neurons, nociceptive specific neurons terminate here. The nociceptive specific neurons respond only to nociceptive stimulus. WDR neuron responds to both non-nociceptive and nociceptive stimuli. Both types of neurons are believed be important in the perception of nociceptive information. Chronic pain conditions are explained in terms of the input to these cells and their supraspinal connections.



NeuroPlasiticity:

Neuroplasticity describes the dynamic modulation of the neural impulses. As the peripheral nerve firing increases there is some functional changes also occurs in the excitability of spinal cord neurons and altering their responses to afferent impulses.

Wind-up phenomenon:

The temporal summation of number and duration of action potentials elicited per stimulus that occurs in the dorsal horn neurons has been referred to as wind-up phenomenon. This result in persistence of action potential for up to sixty seconds after stopping the stimulus and results in change in spinal cord processing that can lasts for one to three hours. Spinal cord synaptic plasticity involves binding of glutamate to NMDA receptors as well as substance P and neurokinins. Binding of glutamate to NMDA receptors

alters magnesium dependent block of iron channels , which increases permeability to all cations particularly Na^+, Ca^{2+} , furthermore glutamate activates AMPA receptors which control depolarization primarily through modulation of Na^+ influx into cells. In addition to modulating augmented excitability these transmitters, cellular mechanism mediate changes in postsynaptic cells leading to permanent changes in nerve conduction.

Transmission and modulation:

Dorsal horn and its laminae act as receiving site action potential coming from periphery via primary afferent neurons. The primary afferents terminates in the dorsal horn and synapse with secondary afferent neurons. The secondary afferent neurons act as gate cells providing initial modulation of action potentials in the dorsal horn. Two main classes of neuro-transmitters associated with primary afferent nociceptive transmission in the dorsal horn

1. Excitatory amino acids e.g., Glutamate
2. Neurokinin peptides e.g., Substance P

Perception:

Thalamus and cortex:

After leaving the dorsal horn nociceptive action potentials ascends through spinothalamic tract , spinocervical tracts , Spino reticular tracts and spino mesencephalic tracts and reach higher centers like cerebral cortex , hypo thalamus reticular formation and mid brain. Afferent impulses to reticular area and activates this area which then send signals through thalamus and cerebral cortex. This alerts the individual to continuous tissue damage and awakens the person from sleep. These signals are poorly localized and helps only to alert the individual.

NMDA receptors :

NMDA receptors are postsynaptic to primary afferent neuron and located on secondary afferent neurons. They are blocked by Mg^{2+} ions under normal conditions the secondary afferent neurons are not depolarized along enough to dislodge the mg^{2+} ions from the ion channels to permit ca^{2+} ions. Glutamate rapidly removed from the synaptic cleft and there is no activity at NMDA receptors in normal nociceptive transmission. But in the presence of pain arising from abnormal conditions like neuropathic pain, chronic pain peripheral sensitization, the frequency of pain signals increase as which in turn increases the amount glutamate. This glutamate depolarize the secondary afferent neuron long enough to dislodge the Mg^{2+} which blocking the NMDA receptors. Subsequent activation NMDA receptors acts to activate second messengers , enzyme systems and various substances like nitric oxide that contributes to enhanced sensitivity known as central sensitization . The activation of NMDA by glutamate also activates protein kinase-C, which causes uncoupling of opioid receptors system results in decreasing responsiveness which is called opioid tolerance.

Types of pain:

Qualitatively there are two types of pain

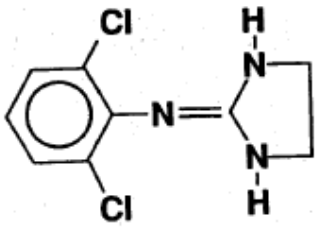
1. Fast pain - is short, well localized, stabbing sensation that is matched to the stimulus like in pin prick, surgical incision. This pain starts abruptly when the stimulus is applied and stops when the stimulus is removed. This is due to stimulation of small myelinated A δ fibers with conduction velocities of 12 to 30 m/s. Myelination provides junctions that permit the electrical impulses to jump which results in rapid transmission.

2. Slow pain- is throbbing, burning or aching sensation that is poorly localized and poorly matched to stimulus . This is due to stimulation of unmyelinated C -fibers with conduction velocity of 0.5 to 2 m/s.

Clonidine

Pharmacology and Pharmacodynamics

It is a 2, 6 - dichloro phenyl - 4, 5 dihydro- 1H-imidazol-2 amine with formula $C_9H_9Cl_2N_3$. It is an imidazoline derivative and acts on both α_1 and α_2 receptors with ratio of α_2 and α_1 are 220:1. It stimulates α_2 receptors both at central and peripheral sites. It is not a pure α_2 agonist and it also acts on non-adrenergic imidazoline preferring receptors.



(clonidine)

Sub types of α_2 receptors:

1) α_{2A} 2) α_{2B} and 3)α_{2C}

α_{2A} - mediates sedation, sympatholysis, analgesia

α_{2B} - vasoconstriction, anti-shivering mechanism

α_{2C} - Sturtle response. It is the response of the body and mind to sudden unexpected stimuli e.g. a flash of light.

Mechanistic information:

α_2 receptors are located on primary afferent terminals (both peripheral and spinal endings) on neurons in superficial laminae of the spinal cord and within the brainstem nuclei implicated in analgesia[9] , supporting the possibility of analgesic action at periphery , spinal and brainstem sites. Notably the axons of peripheral nerves or lacking the α_2 receptors , but Clonidine produces minor degree of conduction blockade at higher concentration with some preference to 'C' fibers[10,11] . This action may underlie in part, in the enhancement of peripheral nerve block when this agent added to the local anesthetics.

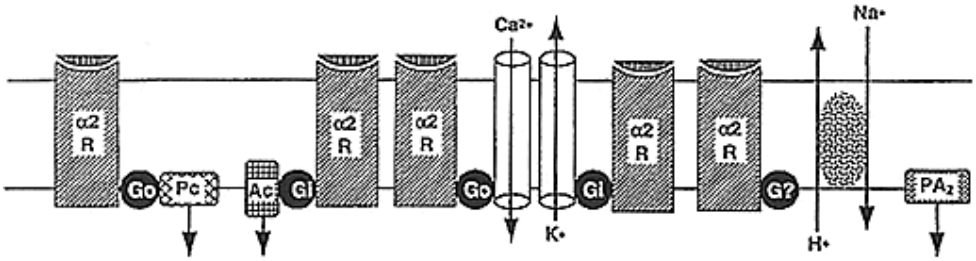


Figure 1. Cellular mechanism of alpha-2 agonists.

α2-R = alpha-2 agonist receptor	Ac = Adenylyl cyclase
G_i = Inhibitory G-protein;	Pc = Phospholipase C
G_0 = Activating G-protein	PA_2 = Phospholipase A_2.

Analgesia produced by intrathecal Clonidine is not produced by systemic absorption because the peak levels in arterial blood is achieved within 10 minutes and in intravenous blood is within 30 to 45 minutes elimination from the blood is slow and the duration analgesia is relatively brief and this point is arguing against an action by systemic absorption and redistribution to central and peripheral sites.

Various routes of administration and dosage

ROUTE	DOSE
intra nasal	2 – 4µg/kg
intramuscular	2 µg/kg
oral	4 – 5µg/kg

Intravenous	Bolus: 1 - 2µg/kg Infusion: 0.18—3.16 µg
Rectal	2.5 - 5 µg/kg with atropine 50 µg/kg
Caudal	1 - 2 µg/kg
Spinal adjuvant	1 - 2 µg/kg
Epidural adjuvant	0.0625% bupivacine with fentanyl 1 µg/ml and clonidine 0.6µ/ml at a rate of 0.2 ml/kg/hr
Sciatic nerve block	0.2% ropivacine 0.4 mg/kg/hr with clonidine 0.12 µg/kg/hr as infusion
Para vertebral block	19ml bupivacine as a bolus with Clonidine 150 µg/kg given every 48 hours for 3 weeks via catheter

Comparison between various routes of administration:

As with lipophilic opiods the Clonidine produces it's effect after intravenous, intrathecal, epidural administration but more potent after neuraxial administration than after systemic administration ,this point supporting the spinal site of action of the Clonidine and thus favouring the neuraxial administration of the Clonidine. This is confirmed by one study

in which small dose of Clonidine (150µg) in intrathecal route provides 4 - 6 hrs of analgesia in case of caesarean section or minor orthopedic surgery, but the same dose of Clonidine by intramuscular route or epidural route produces no more analgesia than placebo.[15,16]

Comparison of epidural and intravenous routes of administration:

Larger dose of Clonidine through epidural administration produces better analgesia and accompanied by 50% reduction in morphine requirements. These results are in accordance with spinal site of action[15,16]

In second type of study, the patients were allowed to titrate the drug to get a similar degree of pain relief via PCA to compare the potency of the drug by different routes of administration. By using this method Bernard and colleagues[18] recently demonstrated the Clonidine is approximately 2 times more potent in epidural route than intravenous.

Confirmation of the receptor site:

Yohimbine, an α_2 antagonist produces at least partial reversal of epidural analgesia and sedation although the effects on blood pressure and heart rate were not reversed[19].

Acetylcholine and neuraxial Clonidine:

Epidurally administered Clonidine produces increase in a release of acetylcholine in the dorsal horn of the spinal cord, but not in the ventral horn.

Analgesia produced by the epidural Clonidine in volunteers is enhanced by the intrathecal injection of choline-esterase inhibitor neostigmne. This interaction is additive only in humans, but synergistic in animals. This supports the cholinergic mechanism in spinal analgesia

produced by the Clonidine. The descending nor-adrenergic pathways release nor-adrenaline to cause analgesia directly and by stimulating the release of acetylcholine.[12,23]

Clonidine and local anaesthetics:

Clonidine enhances both sensory and motor blockade produced by the local anaesthetics by three possible mechanisms

1. Clonidine blocks the conduction in the "C" fibers and in the "Aδ" fibers and increases the K^+ ion conductance in isolated neurons in-vitro and it intensifies the conduction blockade produced by the local anesthetics, because the systemic pharmacokinetics are not the factor in vitro experiments. These data supports the direct effect of the Clonidine on neural transmission in high local concentration.

2. Clonidine may produce vasoconstriction and thereby inhibiting the removal of the local anaesthetics surrounding the neural tissues, but this occurs only in high concentrations and there is little evidence for this mechanism with clinically used concentrations and this is confirmed by the observation that the plasma lignocaine concentrations is same with or without Clonidine addition, but this plasma lignocaine concentrations is reduced because of decreased systemic absorption[10, 11, 24] .

Hemodynamic effect:

Clonidine is lipophilic so that there is rapid and extensive systemic absorption following spinal administration and the hemodynamic effects are in part ,due to it's actions at both central and peripheral nervous system. It affects blood pressure in a complex manner because it has opposing actions at multiple sites.[28,29]

1. In the nucleus tractus solitarius and locus cerulius of the brain stem the Clonidine causes activation of post synaptic α_2 noradrenergic receptors and reduces the sympathetic drive.

2. It is not a pure α_2/α_1 agonist, and also it activates non-adrenergic imidazoline preferring receptors which are present in the lateral reticular nucleus and thereby producing hypotension and anti-arrythmic action[30,31].

3. In the peripheral nervous system it activates α sub2 adrenoceptors at sympathetic terminals and reduces nor-adrenaline release from these terminals ,which could cause vaso relaxation and reduces the chronotropic drive. These brainstem and peripheral α_2 adrenoceptor stimulation are counterbalanced by direct peripheral vasoconstriction from circulating concentrations of α_2/α_1adnergic agonist, clonidine.[32]

In addition to the brainstem, peripheral sites of actions the neuraxial administration of the clonidine directly inhibits the pre-ganglionic sympathetic neurons in the spinal cord[33] especially in the upper thoracic level of injection (which produces more profound hypotension)[34,35] but at the lower thoracic level of administration, Clonidine is not associated with increased incidence of hypotension[17]. Increased incidence with upper thoracic injection perphaps reflects the rostrocaudal gradient of noradrenergic innervation of sympathetic pre-ganglionic fibers.

Action of the clonidine on myocardial proformance:

I) Produces bradycardia partly due to vagomimetic action and partly due to pre-synaptically mediated inhibition of nor-adrenaline release at neuroceptor junction Although it depresses the AV nodal conduction, severe brady arrythmias are rare with Clonidine.

II) It increases the cardiac output by reducing the afterload, but in some partients, it reduces cardiac output due to the decrease in the heart rate.

III) It reduces the Oxygen demand and has been shown to reduce the infarct size when administered to the patients in the acute phase of myocardial infarction. Haemodynamic effects after neuraxial or systemic administration starts within 30 minutes and reaches the

maximum effect within 1 to 2 hours and lasts for approximately 6 to 8 hours after single injection. Delayed onset of hypotension has not been observed with the use of Clonidine for analgesia alone or in combination.[36]

Hemodynamic effects:

This combination produces higher degree of sympatholysis and the combination of Clonidine and local anesthetics in neuraxial route and resulting hypotension is also high. Clonidine has minor or no effects on responses to vasoconstrictors or atropine given to treat hypotension or bradycardia that may occur with neuraxial anesthesia[36]. Clonidine pre-treatment delays the central nervous system or cardiovascular system toxic manifestations of Bupivacaine overdose and also it improves ventricular electrophysiologic parameters in dogs. But this is not to imply that Clonidine should be used as treatment for Bupivacaine overdose, but rather to emphasize that, should such overdose occur, inclusion of Clonidine is unlikely to exacerbate the problem. Spinal neostigmine counteracts the hypotension induced by Clonidine due to cholinergically mediated increase in pre-ganglionic sympathetic neuron activity and it also enhances analgesia produced by Clonidine. This combination may be useful clinically[23, 37].

Sedation:

It commonly occurs after neuraxial administration of the Clonidine. After epidural administration, Clonidine by its systemic absorption and vascular redistribution to higher centers produces sedation[38].

Site of action:

The brain stem nuclei called as locus ceruleus, which is involved regulation of sleep, wakefulness. It is inhibited by G Protein mediated mechanism that involves inhibition of adenyl cyclase.[38]

Dose Dependent Sedation:

Regardless of route of administration the Clonidine produces rapid sedation in less than 20 minutes over the dose range of 50-900 µg. After a large epidural bolus dose (700 µg.) sedation is intense for 4 - 6 hours and reduced the need for other sedatives, anxiolytics when Clonidine given intraoperatively.[40]

Unique feature of sedation:

The Clonidine produces arousable sedation but with other drugs which acting on GABA receptor produces clouding of consciousness and causes paradoxical agitation.

Respiratory depression:

Although the respiratory depression produced by narcotics may be due to noradrenergic mechanism which is supported by some evidence. Clonidine alone do not induce respiratory depression even with massive doses[41] and not potentiate the depression produced by narcotics[42]. Occasional reports of upper airway obstruction during deep sedation with Clonidine and which is accompanied by transient fall in oxygen saturation. So that monitoring the patients with pulse-oxymetry may be needed for 30 minutes to 2 hours after large bolus doses.

Hormonal effects:

As it is a potent sympatholytic agent, it reduces but not suppresses the stress hormones like nor-adrenaline, adrenaline, ACTH, cortisol.

It promotes the release of growth hormone[45], but the effect is short lived. This also reduces the insulin release by direct action on islet cells, but it is clinically

insignificant[14]

Mechansim of antishivering effect:

The clonidine synchronously decreases the cold-response threshold while slightly increasing the sweating threshold and thus suggesting that it acts on central thermal regulatory system rather than preventing shivering peripherally.

Duration of Analgesia and Blood pressure effect of Epidural clonidine alone after surgery:

The common side effects after epidural Clonidine are

1. hypotension
2. bradycardia
3. drymouth
4. sedation

Epidural Clonidine produces dose dependent reduction in blood pressure and a 5 – 20 % reduction in heart rate. In one study 181 patients received bolus epidural Clonidine after non obstetric surgery only 1% of patient received atropine for treatment of bradycardia and many patients received intravenous fluids for reduced blood pressure, none received intravenous vasoconstrictors. But in contrast none of 92 patients received epidural Clonidine by continuous infusion or PCA required atropine for bradycardia. But 8 patients (9%) received vasoconstrictors for hypotension. Sedation is common with bolus administration and lasts for 1 – 2 hours after 150 µg. and 2 - 4 hours after 400 µg. But sedation is uncommon with continuous infusion. But in all patients there is no evidence of respiratory

depression by pulse oxymetry, PaCo2, ETCO2, or respiratory rate monitoring. Epidural Clonidine, along with local anesthetics (150 µg. Clonidine + 9 ml. 0.25% Bupivacaine) during total hip replacement under general anesthesia, doubled the duration of post operative analgesia. When compared with Bupivacaine alone.[54]

***Urinary retention and Clonidine**:*

Intrathecal opioids may produce urinary retention, but does not produce urinary retention but it may actually hastens the time to first micturition after spinal anesthesia[65,67]

Blood and C.S.F pharmacokinetics of epidurally administered Clonidine:

In contrast to the blood, there is a strong correlation between the Clonidine concentration in C.S.F and analgesia after epidural administration, the concentration which produces EC_{95} (95% maxmimal effect) 130ng/ml and when this level is reached in the C.S.F. the P.C.A. approaches zero[12, 13]

Parasympathetic system and Clonidine:

Clonidine produces bradycardia, AV nodal conduction delay may also occurs but not to the level to produce bradyarrythmias. Vasoconstriction, anti-shivering mechanism due to direct action on postsynaptic α_2 receptors present in the vascular smooth muscle.

Absorption:

It is well absorbed by all the routes - oral, intravenous, intramuscular, transdermal etc. The bioavailability is nearly 100% by oral route. Elimination half-life of 6 to 12 hours with the mean of 12 hours, about half the drug administered is excreted unchanged through urine and the half life of the drug is increased with renal failure.

Metabolism:

The 50% of the drug is metabolized in the liver to inactive metabolites which are excreted in the urine.

Drug interactions:

Tricyclic antidepressants and presumably phenothiazines and butyrophenones interfere with the action of Clonidine, but butyrophenone administration may produce hypertensive crisis at least theoretically, even though none has been reported. Acute Clonidine administration reduces anesthetic requirements by 40 to 60%.chronic administration reduces by 10 to 20%.

Uses:

1) as a pre-anesthetic medication
2) helps to reduce the stress response
3) helps to treat the withdrawal symptoms of alcohol, narcotics, tobacco as it reduces sympathetic manifestations of withdrawal

4) to treat the post menopausal hot flushes.
5) to reduce the anesthetic requirement that is M.A.C. up to 95%
6) helps to differentiate the pheochromocytoma and hypertension .
7) helps to treat both intra-operative and postoperative shivering .
8) improves the diarrhoea due to autonomic neuropathy.
9) central neuraxial placement of clonidine alone or along with
10) local anesthetics produces analgesia.
11) To treat the postural hypotension as it has direct action on vascular smooth muscle

Side effects:

1) excessive sedation in higher doses produces upper airway obstruction and decrease in oxygen saturation.
2) dryness of the mouth
3) contact dermatitis if it is used as a transdermal patch
4) sexual dysfunction
5) abrupt withdrawal in hypertensive patients leads to hypertensive crisis.

Pharmacology of Bupivacaine

Bupivacaine is an amide linked local anaesthetic. It is a hydrochloride salt of d (1) -1 - butyl 2,6 pipecoloxylidide and is presented as a racemic mixture. First report of its use was published in 1963 by Telivuo. It is derived from Mepivacaine and is very stable compound and may be autoclaved repeatedly.

Pk_a - 8.1; MW - 288

Protein binding - 95%

Lipid solubility - 28

Elimination half life - 210mts

Toxic plasma concentration >1.5 (µg/ml)

Approximate duration of action - 175mts

Dosage - Maximum dosage 3mg/kg body weight.

Uses:

1. Spinal anaesthesia
2. Epidural anaesthesia
3. Caudal anaesthesia
4. Continuous epidural anaesthesia
5. Peripheral nerve block

Pharmacokinetics:

Once injected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

High lipid solubility of Bupivacaine makes it easy for nerve and vascular tissue penetration. 80-95% of the absorbed Bupivacaine binds to the plasma.

Distribution:

Rapid distribution phase:

In this phase the drug is distributed to highly vascular region t1/2 being 2.7 minutes.

Slow disappearance phase:

In this phase the drug distributes to slowly equilibrating tissues t1/2 being 28 mts.

Biotransformation and excretion phase:

T1/2 is 3.5hours

Clearance is 0.47 litres/minute.

Biotransformation:

Possible pathways of metabolism of Bupivacaine include aromatic hydroxylation and conjugation. Only the N-dealkylated metabolite, N-desbutyl bupivacaine has been measured in blood (or) urine after epidural (or) spinal anaesthesia. Alpha1 acid glycoprotein is the most important plasma protein binding site of Bupivacaine and its concentration is increased by many clinical situation including post operative trauma.

Excretion: is through the kidney, 4-10% of the drug is excreted unchanged.

Mode of Action:

a) *Site of action*:

The spinal nerve rootlet fine nerve filaments having a large surface area are exposed to the local anaesthetics. Posterior and lateral aspects of the spinal cord itself.

b) *Sodium Channel blockade*:

They impede sodium ion access to the axon interior by occluding the transmembrane sodium channels thus delaying the process of depolarization and axon remains polarized. It is a non-depolarization blockade.

Pharmacodynamics:

It has got a longer duration of action but a slower onset.

Cardio vascular system:

It reduces cardiac output by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return, it produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound.

It produces a fall in central venous pressure. It causes an increase in lower limb blood flow. It causes a reduction in incidence of deep vein thrombosis.

Respiratory System:

Spinal blockade seldom, if ever causes respiratory problem.

Gastro intestinal tract:

There is an increase in gastro intestinal motility and emptying of the gastric contents is better.

Toxicity:

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity reactions primarily involve central nervous system and cardio vascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central Nervous System Toxicity:

Initial symptom includes feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include shivering, muscle twitching and tremor. Ultimately generalized tonic, clonic seizures occurs.

Cardiovascular System Toxicity:

The rate of depolarization in fast conducting tissue of purkinje fibers and ventricular muscle is decreased. The rate of recovery of Bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

Anatomy of the spinal cord

It is covered by three meninges, the outer most is dura and it extends from the skull where it fuses with foramen magnum The caudal tip is at the level of S_2 segment.

Structure of the dura:

Dura: is composed of collagenous lamellae and elastin elements separated by clefts filled with ground substance which account for permeability.

Arachnoid and pia : Immediately within the dura is the arachnoid matter which encloses the subarachnoid space.

Subarachnoid block means the temporary interruption of nerve transmission within the subarachnoid space produced by injection of a local anaesthetic solution into cerebrospinal fluid.

Applied anatomy of vertebral canal:

Vertebral canal extends from foramen magnum to the sacral hiatus. It protects the spinal cord. The vertebral column comprises of 33 vertebrae (7-cervical, 12-thoracic, 5-lumbar, 5-fused sacral and 4-coccygeal) has four curves. Cervical and lumbar curves are convex anteriorly and thoracic & sacral curves are convex posteriorly. The curves of the vertebral column influence the spread of the local anaesthetic in the subarachnoid space.

Each vertebra is composed of a body separated from the adjacent vertebra by intervertebral disc and vertebral and formed by pedicles and laminae, which surround and protect the cord laterally and posteriorly.

The vertebral column is bound together by several ligaments. They are,

1. ***Supraspinal ligament*** passes longitudinally over the tips of the spinous processes from C7 to the sacrum.
2. ***Interspinous ligament*** connects the adjoining spinous processes together.

3. ***Ligamentum Flavum*** known as yellow ligament, connects the adjacent laminae composed of yellow elastic fibers. They become progressively thicker from above downwards.
4. ***Posterior longitudinal ligament*** is on the posterior surface of bodies of vertebral.
5. ***Anterior longitudinal ligament*** runs along the front of the vertebral bodies.

There are seven projections from these vertebral (or) neural arches. They are 3 muscular processes, 2-Transverse processes and 1-spinous process for the attachment of muscle and ligaments. Four articular processes - 2 upper & 2 lower which, in the lumbar region, prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Vertebral canal formed by these structures has deficiencies posteriorly in the midline called inter laminar foramina which enlarge in flexion accessible for the passage of spinal needle. The direction of spinous process determines the direction of spinal needle.

SPINAL CORD

It is the direct continuation of the medulla oblongata extending from the upper border of the atlas to the first lumber vertebra below which there is leash of nerve roots termed cauda equina. Spinal nerves are 31 pairs totally - 8 Cervical, 12 Thoracic, 5 Lumbar, 5 Sacral, 1 Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots uniting at the inter vertebral foramina and form a nerve trunk. Membranes covering the spinal cord from without are dura mater, arachnoid mater and piamater. Dura and arachnoid mater end at S2 level. Piamater is closely applied to the spinal cord.

BLOOD SUPPLY: It is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise from the posterior inferior cerebellar arteries. There is no anastamosis between these arteries.

VENOUS DRAINAGE: The spinal veins are arranged into anterior and posterior plexus which are draining into vertebral, azygos and lumbar veins.

CEREBROSPINAL FLUID

This is an ultra-filtrate of the blood plasma from choroids plexus of the lateral ventricles with a pH of 7.32 (7.27-7.37). It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricle of the brain. The total volume of CSF in an average adult ranges from 120-150ml of which 25-35ml is in the spinal subarachnoid space.

Composition of cerebrospinal fluid:

Specific gravity - 1.006 (1.003-1.009) at 37^0C

Pressure - 60-80mm of H_2O

PCO_2 - 48mmHg

HCO_3 - 23meq/l

Na+ - 133-145meq/l

Ca+ - 2-3meq/l

Po4- - 1.6meq/dl

Mg+ - 2-2.5meq/l

Cl^- - 15-20meq/l

Protein - 23-38mg/dl

Sugar - 45-80mg/dl

Lymphocytes - 0-5cells/cmm

An important factor that determines the spread of drug in cerebrospinal fluid is the specific gravity of the drug in relation to that of cerebrospinal fluid (Baricity) which is 1.003-1.009. Hyper baric solution is one which is denser than CSF at 37^0C.

PHYSIOLOGY OF SUBARACHNOID BLOCK:

Subarachnoid block implies the temporary interruption of nerve transmission within the subarachnoid space by injections of local anaesthetics. The blockade of nerve fibres occur in the order of Temperature, Pain, proprioceptive and then motor fibres.

FACTORS INFLUENCING BLOCK HEIGHT:

a - Site of injection

b - Angulation of needle

c - Characteristic of local anaesthetic

i) Density of local anaesthetic

ii) Specific gravity

iii) Baricity

d - Dose of local anaesthetic

e - Position of the patient during and after injection

f - Anatomic configuration of spinal column.

g - Patient height (at extremes)

h - Reduced cerebrospinal fluid with increased intra abdominal pressure (eg. Pregnancy)

a) Effects on Cardio Vascular System:

Most important physiological responses to subarachnoid block involve cardio vascular system due to combined effect of autonomic denervation, higher level of neural block, added effect of vagal innervation. Local anaesthetics and vasoactive substances administered in small doses intrathercally leads to direct cardiovascular effect. Level of sympathetic denervation determines the magnitude of cardio vascular system responses, but the relationship is neither predictable nor precise.

Sympathetic denervation produces arterial and more physiologically important arteriolar dilatation and vasodilatation in the venous circulation produces fall in blood pressure. Due to loss of Bainbridge reflex, the fall in blood pressure is associated with bradycardia, blockade of cardiac sympathetic fibres from T1-T4 is an additional factor that causes bradycardia.

b) Effects on Respiratory System:

Respiration is not depressed normally. High spinal can cause paralysis of intercostals muscles but resting tidal volume, maximum inspiratory volume, respiratory rate, ABG, negative intrapleural pressure and also the phrenic nerve are unaffected. Hypoxia may accompany hypotension and is corrected by oxygen administration via face mask.

c) Gastro Intestinal Effect:

Pre-ganglionic fibres from T5-L1 are inhibitory to gut. So in sympathetic blockade the small intestine contracts with relaxed sphincters and peristalsis remains normal. Handling of viscera causes discomfort and bradycardia since vagus is not blocked.

d) Hepatic and Renal Effects:

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure. There may be normal hepatic oxygen extraction. Renal blood flow is maintained by autoregulation and does not decrease till mean arterial pressure goes below 50mmHg.

Sphincters of bladder are not relaxed, and tone of ureters is not greatly altered. Urinary retention occurs. Penis is often engorged, and erigentes (S2, S3). Uterine tone is unchanged in pregnancy. In the absence of hypotension spinal anaesthesia has got no effect on the progress of labour and uterine blood flow.

f) Metabolic and hormonal effect:

Spinal anaesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site. It minimizes the rise in blood sugar, coritsol, catecholamines renin and aldosterone release associated with stress. Post operative negative nitrogen balance and secretion of anti-diuretic hormone are inhibited.

g) Thermo Regulation:

Hypothermia results from heat loss to the cold environment due to vasodilatation.

AIM OF THE STUDY

1. To evaluate the efficacy of Clonidine in prolonging the duration of post operative analgesia when combined with Bupivacaine.

2. To study the property of Clonidine to potentiate the analgesic effect of Bupivacaine.

3. To observe the safety of intrathecally administered Clonidine.

REVIEW OF LITERATURE

Bonnet et al [15, 26, 48, 60, 62] studied spinal Clonidine as adjuvant with Bupivacaine in orthopedic surgeries and proved that the combination was effective in preventing the tourniquet pain and effectively prolonging the post-op analgesia.

Fogarty et al[63] compared spinal Clonidine vs morphine with Bupivacaine in patients undergoing total hip replacement surgeries. Intrathecal Clonidine prolonged the duration of spinal analgesia, but was markedly inferior to the intrathecal morphine in providing subsequent postoperative analgesia

Grace et al[3] studied the co administration of Pethidine with Clonidine in spinal anaesthesia for total hip replacement surgeries.

Monica brunschwiller et al compared intraoperative anaesthetic and

haemodynamic effects of clonidine-bupivacaine, morphine-bupivacaine

and placebo-bupivacaine combinations during continuous spinal anaesthesia in knee replacement surgeries and concluded that 0.15 mg Clonidine but not 0.15 mg morphine prolonged surgical analgesia when added to 10 mg plain Bupivacaine.

Pan et al studied the analgesic effects of intrathecal neostigmine vs

Clonidine with Bupivacaine in cesarean section. Their study showed that the

combination of 150 µg Clonidine and 50 µg neostigmine provided longer

post-surgical analgesia than with either drug used alone. However, this combination also produced significantly more adverse effects of prolonged motor block and nausea, vomiting.

Philip .j.siddall et al studied that the efficacy of Intrathecal Morphine and

Clonidine in the treatment of pain after spinal cord Injury. They Demonstrated that administration of a combination of morphine and Clonidine into the spinal fluid can provide substantial pain relief in some people with this type of pain.

Dekock.m.et al [17,34,36,39,53] studied spinal clonidine with ropivacaine in ambulatory knee arthroscopy surgeries. They concluded that Small-dose intrathecal clonidine (15 μg) plus 8 mg intrathecal ropivacaine produces adequate and short-lasting anesthesia for knee arthroscopy.

Debrydnjov I et al [75] have tried 6 mg of 0.5% heavy Bupivacaine with 15μg vs 30μg of Clonidine for unilateral spinal anaesthesia in unilateral inguinal hernia surgeries and showed it have produced excellent post-op analgesia. They concluded that use of Clonidine as adjuvant to small dose 6mg Bupivacaine for ambulatory inguinal herniorraphy.

Michael j. peach et al (*10.(2004) anaes analg., 2004;98;56-59****)*** studied intrathecal fentanyl with morphine and varying doses of Clonidine in cesarean surgeries for post-op analgesia. A multimodal approach to post-cesarean analgesia, using subarachnoid Bupivacaine, fentanyl, morphine 100μg, and Clonidine 60μg, improves pain relief compared with morphine 100μg or clonidine 150μg alone, but increases intra-operative sedation and may increase peri-operative vomiting.

Alain rochette et al studied spinal Clonidine in neonates. Spinal anesthesia is suitable but often too short for complete surgery in newborns. This controlled, randomized, prospective, dose-ranging study was conducted in 75 neonates to test the hypothesis that Clonidine could significantly lengthen Bupivacaine spinal block. He concluded

that Clonidine 1µg/kg, added to spinal isobaric Bupivacaine, doubles the duration of the block without significant deleterious hemodynamic or respiratory side effects.

Van tuiji et al (12. (2006) br. J. an. 97(3); 365-70***)*** have studied the addition of intrathecal clonidine to hyperbaric Bupivacaine on post-op pain and morphine requirements after cesarean section. They concluded that addition of 75µg Clonidine to hyperbaric Bupivacaine 2.2 ml prolongs spinal analgesia and motor block after cesarean section and improves early analgesia without any clinically relevant maternal or neonatal side effects.

B.s.sethi et al (13.(2007) I.J.A) have studied the efficacy of low dose intrathecal Clonidine as adjuvant to bupivacaine in gynaecological surgeries. They have added 1µg/kg of Clonidine with 2.5 ml of Bupivacaine vs plain Bupivacaine. .They concluded that by adding Clonidine, the post op analgesia is significantly prolonged with an effect on sedation, heart rate and MAP which does not require any therapeutic intervention.

MATERIALS AND METHODS

Study design:

This study was a randomized prospective comparative study.

Study setting and population:

After obtaining institutional ethical committee clearance, the study was carried out on 70 patients in the OT, Department of Anesthesiology, Tirunelveli Medical College, Tirunelveli, from April to August 2009.

Inclusion criteria:-

Pregnant patients belonging to ASA I and II were randomly selected between 18 to 28 years of age, and weighing between 45-70 kgs.

Exclusion criteria:

1. Patients with systemic illness like diabetes, hypertension

2. Asthmatic, COPD

3. PIH, Patients on anti-hypertensives,

4. Patients with partial block or failed block

5. Height less than 145 cm

6. Procedures ending with hysterectomy or requiring blood transfusion

7. Anemia, bleeding disorders

8. Contraindication to Clonidine

9. Patients with psychiatric problems

10. Patients having spinal deformities

PRE OPERATIVE EVALUATION:-

In all the patients, Age, I.P.No, Body Weight, Baseline vital parameters were recorded. History regarding previous anaesthesia, surgery, any significant medical illness, medications and allergy were recorded. Complete physical examination and Airway assessment were done.

Following laboratory investigations were done:

- Hemoglobin %
- Blood : sugar, urea, S. Creatinine
- S. Electrolytes : Na+, K+
- ECG in all leads

STUDY METHOD:

After getting, informed consent, the patients were randomly allocated into two groups. Group 'B' (n = 35) was taken as Bupivacaine group and Group 'C' (n = 35) as Clonidine group. The 10 point visual analogue pain scale VAPS was explained to the patients.

All the patients were premedicated with Inj. metoclopramide 10mg i.v, and Inj. ranitidine 50mg i.v 1 hour prior to anaesthesia. Standard monitoring was instituted after shifting the patient on the operating table. Baseline measurements of pulse rate, blood pressure and SpO2 were recorded.

An intravenous access was established and the patients were pre-loaded with ringer lactate 10ml/ kg. They were then positioned in the right lateral position on a horizontal table. After strict aseptic precautions, the L3-L4 inter space was identified and a 23 gauge spinal

needle was used for sub-arachnoid placement. 0.5% hyperbaric bupivacaine 10 mg was injected in B group and 0.5% hyperbaric bupivacaine 10 mg + clonidine 75µg was injected in C group. The patients were then turned supine and a wedge placed under the right buttock. The level of sensory blockade was assessed by pin prick and the surgery proceeded after adequate motor and sensory block were achieved. The pulse rate and blood pressure were monitored at an interval of every 2 min till the delivery of the baby and every 5 minutes thereafter. A fall of MAP by 25% from the base line value was considered as hypotension and managed with intravenous fluids, oxygen and Inj. ephedrine in titrated incremental doses.

Post-operatively the patients were instructed to mark a point on the 10 point visual analogue pain scale according to the intensity of pain. The pain relief was graded as follows in VAPS.

Pain Score	**Quality of analgesia**
0 -1	Excellent
2 – 4	Good
5 – 6	Fair
7 – 8	Poor
9 – 10	No relief

The pain score was assessed every hour and the total duration of post operative analgesia was taken as the period from the time of injection of the spinal anesthetic till the first requirement of systemic analgesic medication.

In both groups patients were given the first analgesic medication when the VAPS score was 6 and above. Patients were observed for any side effects like respiratory depression, nausea, vomiting, urinary retention, hypotension, bradycardia for 24 hours.

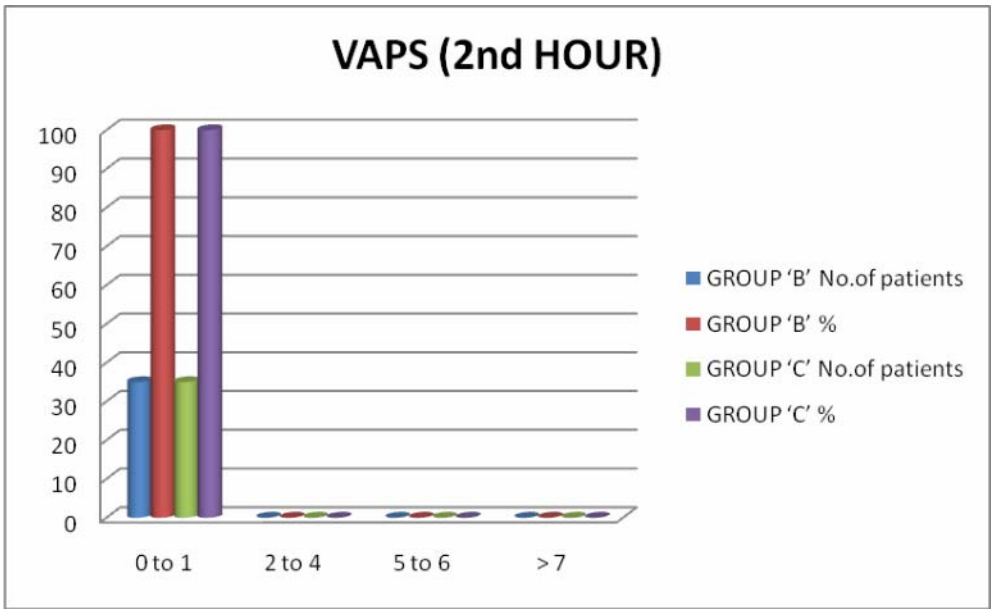
OBSERVATION AND RESULTS

The study was conducted on 70 patients randomly allotted into 2 groups as given below and the VAPS assessed:-

VAP SCORE (2nd HOUR)

PAIN SCORE	GROUP 'B'		GROUP 'C'	
	No.of patients	%	No.of patients	%
0-1	35	100	35	100
2-4	0	0	0	0
5-6	0	0	0	0
> 7	0	0	0	0

After 2 hours post-operatively, both B and C group patients exhibited a pain score of 0 – 1 and were comfortable, manifesting no signs of pain.

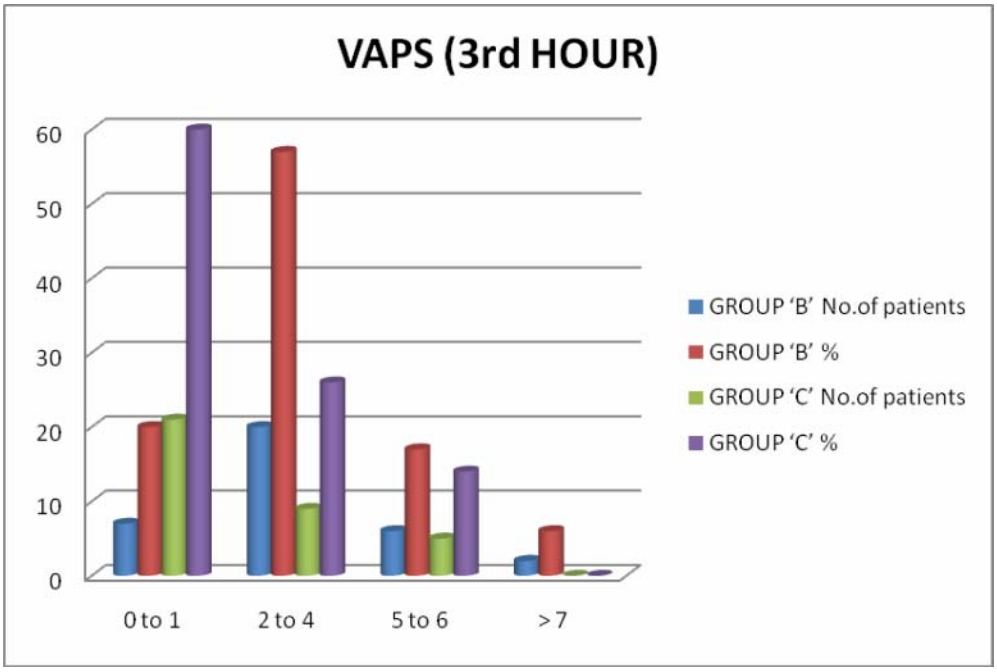


VAP SCORE (3rd HOUR)

PAIN SCORE	GROUP 'B'		GROUP 'C'	
	No.of patients	%	No.of patients	%
0-1	7	20	21	60
2-4	20	57	9	26
5-6	6	17	5	14
> 7	2	6	0	0

After 3 hrs, 8 patients in group B manifested mild to moderate levels of pain requiring systemic analgesic supplementation.

In group C only 5 patients manifested pain which required analgesic supplementation.

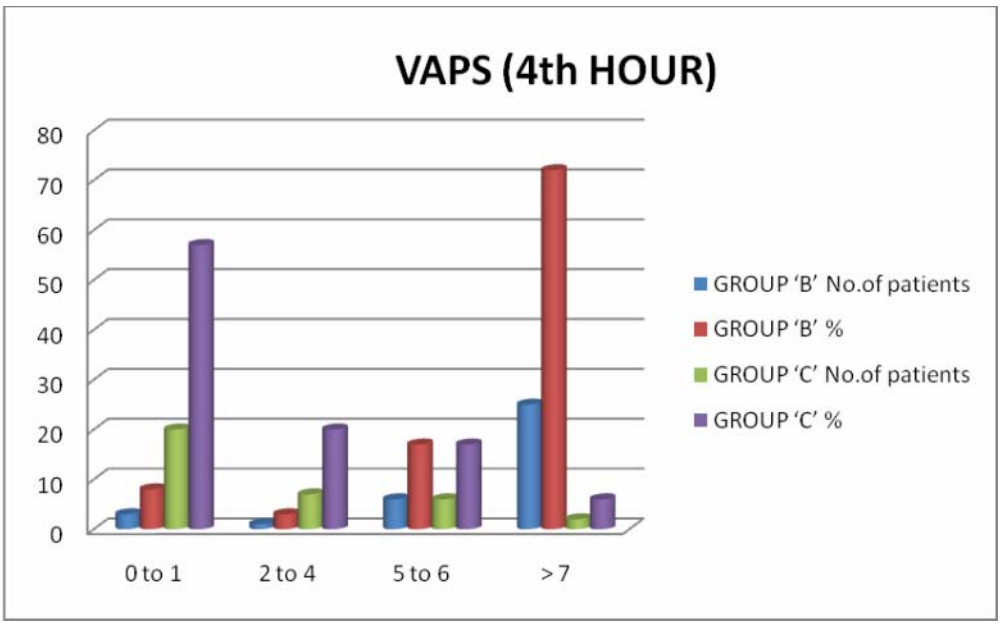


VAP SCORE (4th HOUR)

PAIN SCORE	GROUP 'B'		GROUP 'C'	
	No.of patients	%	No.of patients	%
0-1	3	8	20	57
2-4	1	3	7	20
5-6	6	17	6	17
> 7	25	72	2	6

After 4 hrs, 31 patients in group B manifested pain requiring systemic analgesic supplementation.

In group C only 8 patients manifested pain which required analgesic supplementation.



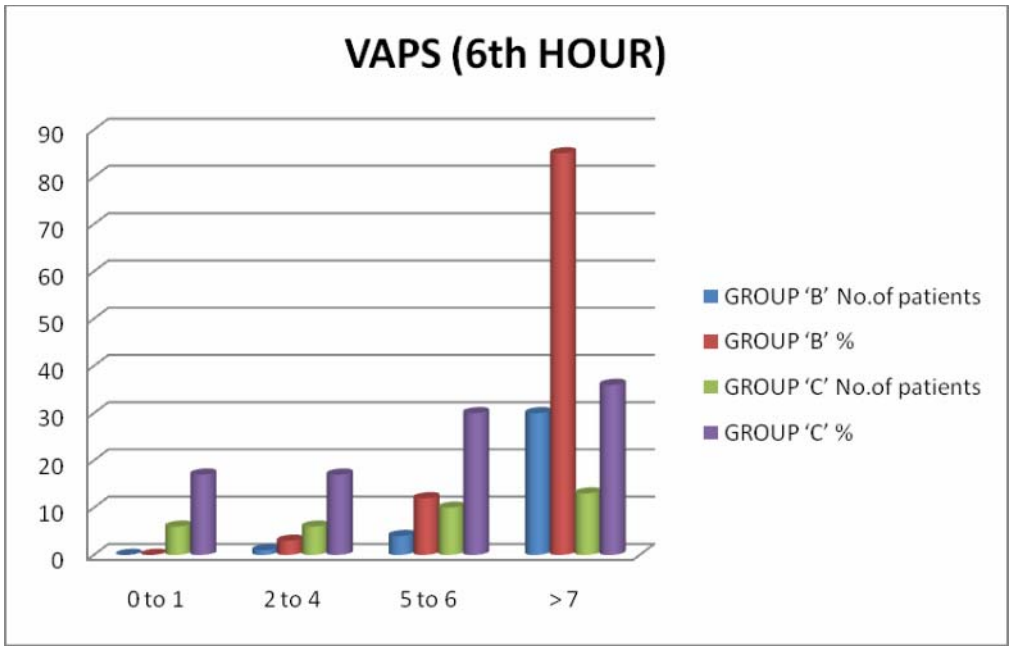
VAP SCORE (6th HOUR)

PAIN SCORE	GROUP 'B'		GROUP 'C'	
	No.of patients	%	No.of patients	%
0-1	0	0	6	17
2-4	1	3	6	17

5-6	4	12	10	30
> 7	30	85	13	36

After 6 hrs, 34 patients in group B manifested pain, with almost 97% requiring systemic analgesic supplementation.

In group C only 23 patients manifested pain, with an average only 66% required analgesic supplementation. 12 of the patients did not show any sign of pain, which is 34% of the study group had good analgesic effect even after 6 hrs duration.



STATISTICAL ANALYSIS

The clinical trial clients had been matched for comparison in respect of their age and body weight by computing mean and SD. The significance of the mean ages was interpreted by UNPAIRED‘t’ test. Duration of pain relief, two segment regression and the hemodynamics like MAP, PR, SPO2 were measured at different time periods and compared between the ‘B’ and ‘C’ group by mean and SD and interpreted by students unpaired ‘t’ test.

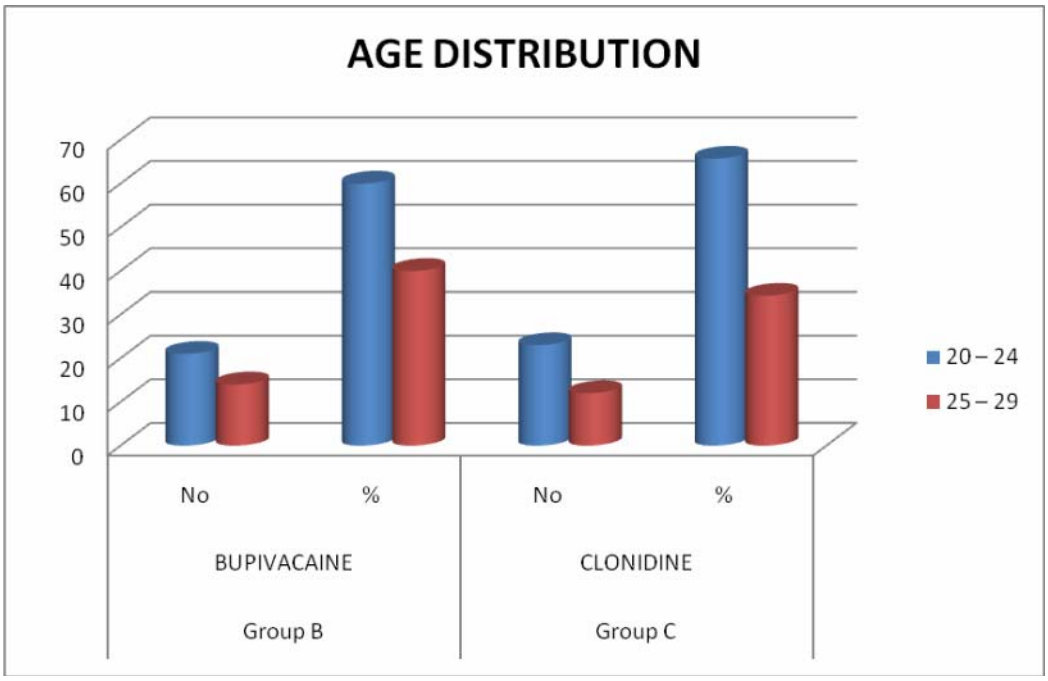
The above statistical procedures were undertaken by SPSS (130) at 5% level of significance (P = 0.05). The clients were matched in respect of their age and weights for comparison of the effect of two drugs (B and B+C) since the two variables were termed as independent variables and which were responsible for the pain relief.

MATCHING OF THE TWO GROUP BY THEIR AGE

AGE GROUP	Group B	Group C

YRS	BUPIVACAINE		CLONIDINE	
	No	%	No	%
20 – 24	21	60	23	65.7
25 – 29	14	40	12	34.3
TOTAL	35	100	35	100
MEAN	23.4		23.3	
SD	1.9		1.9	
't'	0.369			
Significance	P > 0.05			

The mean ages between the two groups were 23.4 ± 1.9 and 23.3 ± 1.9 for B and C group respectively. The difference between two mean ages was not statistically significant (P > .05).

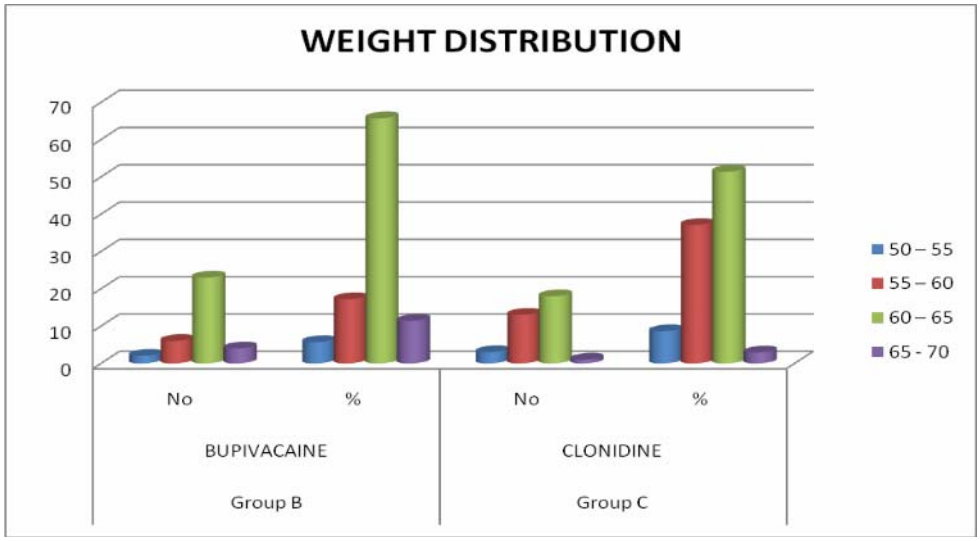


Matching of the B and C group with reference to their body weight

WEIGHT KGs	Group B BUPIVACAINE		Group C CLONIDINE	
	No	%	No	%
50 – 55	2	5.7	3	8.6
55 – 60	6	17.2	13	37.1
60 – 65	23	65.7	18	51.4
65 - 70	4	11.4	1	2.9
TOTAL	35	100	35	100
MEAN	61.1		59.7	
SD	3.2		3.5	

't'	1.734
Significance	P > 0.05

The mean weights between the two groups were 61.1 ± 3.2 and 59.7 ± 3.5 for B and C group respectively. The difference between two mean weights was not statistically significant (P > 0.05).



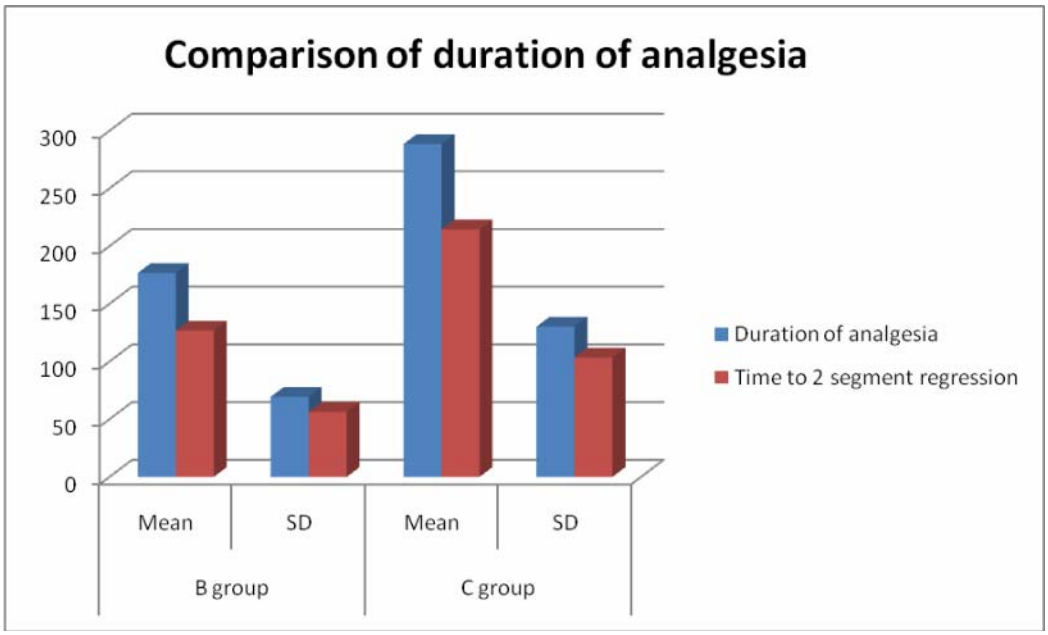
The two groups were matched with reference to their age and weight and they were amenable for comparison of other variables like duration of analgesia, 2 segment regression, MAP, PR, SPO2.

Comparison of duration of analgesia

CATEGORY	N	B group		C group		Mean Difference	't'	Diff	significance
		Mean	SD	Mean	SD				

Duration of analgesia	35	176.9	69.5	288.6	130.3	111.7	4.475	68	P < 0.01
Time to 2 segment regression	35	126.8	56.5	214.6	103.5	87.8	3.955	68	P < 0.01

The mean “duration of analgesia” and mean “Time to 2 segment regression” between the two groups were statistically significant (P < 0.01).



Comparison of hemodynamic variables between the two groups

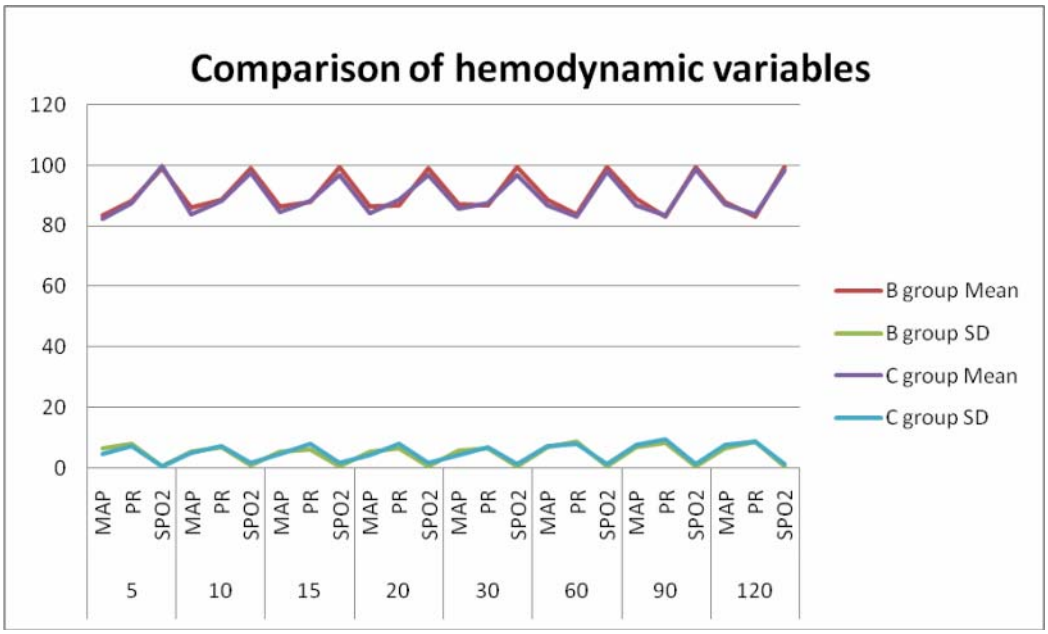
Time Mins.	MEASURES	n	B group		C group		Mean Difference	‘t’	Diff	significance
			Mean	SD	Mean	SD				
5	MAP	35	83.4	6.4	82.5	4.5	0.9	0.669	68	P > 0.05
	PR	35	88.2	8.1	87.8	7.2	0.4	0.234	68	P > 0.05

	SPO_2	35	99.4	0.6	99.9	0.4	0.5	4.407	68	P < 0.01
10	MAP	35	86	5.5	84	5	2	1.604	68	P > 0.05
	PR	35	88.9	6.9	88.6	7.4	0.7	0.548	68	P > 0.05
	SPO_2	35	99.4	0.7	97.7	1.7	51.7	5.376	68	P < 0.01
15	MAP	35	86.6	5.3	84.9	4.7	1.7	1.425	68	P > 0.05
	PR	35	88	6.3	88.3	8.1	0.3	0.148	68	P > 0.05
	SPO_2	35	99.5	0.5	96.8	1.4	2.7	10.791	68	P < 0.01
20	MAP	35	86.5	5.4	84.5	4.2	2	1.687	68	P > 0.05
	PR	35	86.8	6.4	88.8	8	2	1.17	68	P > 0.05
	SPO_2	35	99.4	0.6	97.1	1.4	2.3	8.963	68	P < 0.01
30	MAP	35	87.4	5.8	86	4.4	1.4	1.14	68	P > 0.05
	PR	35	87	6.5	87.7	6.9	0.7	0.393	68	P > 0.05
	SPO_2	35	99.5	0.6	96.9	1.3	2.6	10.882	68	P > 0.01
60	MAP	35	88.8	7	87	7.2	1.8	1.054	68	P > 0.05
	PR	35	83.7	8.7	83.2	8.2	0.5	0.239	68	P > 0.05
	SPO_2	35	99.5	0.6	98	1.2	1.5	6.948	68	P > 0.05
90	MAP	35	89.2	6.9	86.8	7.7	2.4	1.351	68	P > 0.05
	PR	35	83.1	8.6	83.6	9.6	0.5	0.223	68	P > 0.05
	SPO_2	35	99.5	0.5	98.8	1.1	0.7	3.66	68	P < 0.01
120	MAP	35	87.9	6.5	87.4	7.8	0.5	0.283	68	P > 0.05

	PR	35	83.2	8.8	83.9	9	0.7	0.349	68	P > 0.05
	SPO_2	35	99.6	0.5	98.5	1.3	1.1	4.514	68	P < 0.05

The hemodynamic variables such as MAP, PR did not significantly differ at all the time periods of monitoring (5, 10, 15, 20, 30, 60, 90,120).

The SPO2 of B group was lesser than C group at 5^{th} minute only. In all other time periods, the SPO2 of the C group was lesser than B group which is statistically significant, though it is not clinically significant.



DISCUSSION

Clonidine added to Bupivacaine for spinal anaesthesia in Caesarean section improves the analgesia in the immediate postoperative period. The effective dose range of intrathecal Clonidine for post-op analgesia is not known to date. Actually all effects of Clonidine including analgesia are dose dependent. The present study suggests that compared to Bupivacaine alone, the addition of 75 µg Clonidine to Bupivacaine produced a strong analgesia with a mean duration of 288 mins. Furthermore our patients were not

administered any additional opioids or tranquilizers peri-operatively that may have potentiated the analgesic action of Clonidine.

Coombs et al suggested the combination of intrathecal Clonidine 150µg and morphine produced analgesia for 8 hrs.

Van Tuiji et al studied the effect of addition of intrathecal Clonidine to hyperbaric Bupivacaine on postoperative pain and morphine requirements after Caesarean section. He demonstrated that addition of 75 µg Clonidine to

hyperbaric Bupivacaine prolongs spinal analgesia and the motor block after caesarean section and improves early analgesia.

In the present study using Clonidine 75µg alone the analgesia lasted for a mean of 288 mins. The dose is lesser than that used by Coombs et al, but the duration of analgesia is closer to that study even without opioid.

Mondez et al [13]used epidural Clonidine in doses of 400 and 800µg for caesarean section and they found that 800µg group had 5 hours of median duration of analgesia and this is closer to this present study.

The present study shows that the intrathecal route required lesser dose than epidural route but with same duration of analgesia and is safer with no side effects.

Kriton S.Filos et al [73] 150,300,450 µg intrathecal Clonidine for its haemodynamic effects. They found the 300 and 450 µg group had haemodynamic stability, but the 150µg group presented with immediate fall in MAP but with no delayed fall in this group. There was no incidence of significant bradycardia in all the three groups.

The present study with 75µg Clonidine also showed no significant haemodynamic changes. Moreover it had no measurable deleterious side-effects in mother. Although MAP was lower in the C group, this apparently was not considered clinically important, as the fall in MAP was manageable with I.V. fluids and the occurrence of bradycardia was not significantly different between the two groups. Furthermore, the average MAP did not decrease > 25% from baseline.

SUMMARY

The addition of 75 µg Clonidine to Bupivacaine produced a strong analgesia with a mean duration of 288 minutes (4 – 6 hrs). This extended analgesia offered by the studied dose was clinically and statistically significant, at the same time providing hemodynamic stability. The arousable sedation offered by the intrathecal administration of clonidine was

also beneficial, requiring less and infrequent supplementation of systemic analgesics. Moreover, the side effects observed were no greater than that of administration of bupivacaine alone. In fact respiratory depression, urinary retention or pruritus were not even noted in any case, which otherwise would have been an embarrassing side effect of intrathecal opioid.

CONCLUSION

The present study has demonstrated that addition of 75 µg Clonidine to hyperbaric Bupivacaine prolongs post op analgesia and the two segment regression after Caesarean

section, without clinically significant haemodynamic derangements or any adverse effects. Hence intrathecal clonidine along with bupivacaine proves to be a safer alternative to intrathecal opioids and with a dose of 75 µg, the hemodynamic profile is also very acceptable. Thus intrathecal clonidine 75 µg not only potentiates and prolongs the analgesic effect of bupivacaine, but also has a good safety profile for intrathecal use. From this study it could be concluded that addition of 75µg of Clonidine to hyperbaric Bupivacaine is safe and beneficial to pregnant patients posted for LSCS.

MASTER CHART: GROUP C – CLONIDINE

S.No	NAME	AGE	WT	DURATION	VAPS				INITIAL BLOCK	2 SEG REG	CC
					2nd hr	3rd hr	4th hr	6th hr			Na Vo
1	Shanbagam	22	50	135	1	5	X	X	T5	90	NIL
2	Sundari	21	52	317	0	1	4	5	T4	240	NIL
3	Anaanthavalli	20	58	199	0	4	X	X	T4	140	NIL
4	Anathalakhsmi	23	62	147	1	5	X	X	T45	11O	NIL
5	Kavitha	25	64	220	0	4	6	X	T4	150	NIL
6	Saraswathi	26	65	245	0	4	6	X	T4	160	NIL
7	Geetha	25	62	315	0	1	4	6	T4	240	Nil
8	Keetha	24	62	240	0	2	5	X	T4	175	Nil
9	Selvi	23	60	160	0	4	5	X	T4	120	NIL
10	Subbulakshmi	22	59	285	0	2	4	5	T4	210	Nil
11	Maharasi	21	57	275	0	2	4	5	T4	200	Nil
12	Sorna	20	58	240	1	4	6	X	T4	190	Nil
13	Vijayalakshmi	21	59	199	1	4	6	X	T4	150	Nil
14	Indira	22	62	421	0	0	2	4	T4	340	Nil
15	Subusfathima	23	64	260	0	2	4	6	T4	200	Nil

16	Petchiammal	25	61	280	0	2	4	5	T4	205	Nil
17	Lakshmi	26	62	290	1	4	6	X	T4	210	Nil
18	Revathi	26	59	222	0	4	6	X	T4	15	N[l
19	Kalanjium	25	57	293	0	2	4	7	T4	210	Nil
20	Grace	22	58	422	0	0	2	4	T4	320	Nil
21	Muthuparvathi	26	55	392	0	0	2	5	T4	290	Nil
22	Ananthar ubi	25	52	340	0	0	4	5	T4	260	Nil
23	Parvin	24	58	220	0	2	6	X	T4	170	Nil
24	Priya	22	58	210	0	4	6	X	T4	160	Nil
25	Banjana	24	60	155	2	5	X	X	T5	100	Nil
26	Noorali	26	62	210	0	4	6	X	T4	160	Nil
27	Barvani	22	63	720	0	0	0	2	T4	600	NIL
28	Shunmugapriya	21	64	280	0	1	`4	6	T4	200	Nil
29	Subbulakshmi	21	64	280	0	1	4	6	T4	200	NIL
30	Amuthakumari	22	60	460	0	0	2	4	T4	330	Nil
31	Fathima	21	61	280	0	2	4	6	T4	210	Nil
32	Nanada	23	62	255	1	4	5	X	T4	180	NIL
33	Sudha	25	61	255	0	2	4	6	T4	175	Nil
34	Valli	26	59	180	2	4	7	X	T5	110	Nil
35	Sumathi	24	58	700	0	0	0	1	T4	490	Nil

CLONIDINE HEMODYNAMIC PROFILE

S.no	NAME	AGE	MAP									PULSE RATE						
			5	10	15	20	30	45	60	90	120	5	10	15	20	30	4	
1	Shenbagam	22	73	72	74	78	80	70	68	68	68	96	90	84	86	85	9	
2	Sundari	21	88	83	86	82	86	94	94	88	99	92	93	96	98	97	8	
3	Anaanthavalli	20	76	78	80	83	82	82	83	87	87	68	69	74	88	86	7	
4	Anathalakhsmi	23	80	83	87	87	90	96	97	96	98	91	94	102	104	100	9	
5	Kavitha	25	83	79	92	89	92	80	78	76	76	88	89	90	86	92	8	
6	Saraswathi	26	87	86	86	89	88	85	86	87	84	90	92	90	96	86	7	
7	Geetha	25	81	87	85	82	83	93	95	96	95	92	94	96	92	91	8	
8	Keetha	24	93	95	92	88	92	97	93	91	96	92	93	94	95	96	8	

9	Selvi	23	84	83	82	81	86	86	90	87	90	91	92	93	86	84	8
10	Subbulakshmi	22	80	83	86	83	81	82	86	92	83	91	92	90	84	84	8
11	Maharasi	21	81	86	85	83	85	91	96	96	98	98	99	100	97	91\	9
12	Sorna	20	80	85	83	81	82	83	85	82	86	92	86	80	80	80	8
13	Vijayalakshmi	21	85	89	84	92	90	84	84	85	86	90	88	84	86	86	7
14	Indira	22	81	83	83	82	83	78	76	80	82	90	91	87	86	84	8
15	Subusfathima	23	83	81	85	86	84	93	90	86	88	82	80	83	84	86	8
16	Petchiammal	25	80	81	90	86	83	78	78	77	81	88	87	90	91	85	8
17	Lakshmi	26	82	85	92	86	93	96	95	99	94	83	86	87	92	98	9
18	Revathi	26	83	81	80	82	83	86	86	90	88	78	76	79	89	84	7
19	Kalanjium	25	76	80	83	82	92	93	91	94	95	100	102	106	110	100	9
20	Grace	22	93	94	92	90	91	98	97	95	98	86	84	85	83	87	8
21	Muthuparvathi	26	80	79	81	79	83	83	84	81	80	89	90	87	86	90	8
22	Anantharubi	25	76	78	79	82	82	80	78	81	83	76	78	80	81	80	7
23	Parvin	24	85	92	91	93	92	93	92	93	96	91	90	89	87	89	8
24	Priya	22	80	85	81	82	83	78	76	75	80	78	74	70	68	68	7
25	Banjana	24	85	94	90	92	94	95	94	96	91	80	84	86	87	90	9
26	Noorali	26	86	83	86	85	90	93	98	98	98	92	94	95	94	92	9
27	Barvani	22	80	82	82	83	83	80	82	83	85	74	76	77	72	75	6
28	Shunmugapriya	21	83	86	88	90	90	93	89	83	83	87	86	84	88	87	8
29	Subbulakshmi	21	80	83	80	78	78	78	82	78	79	86	84	82	86	82	8
30	Amuthakumari	22	80	80	82	79	84	83	85	90	93	94	96	94	92	87	8
31	Fathima	21	81	80	83	81	82	82	88	80	82	90	84	86	85	86	7
32	Nanada	23	84	87	93	90	89	93	89	92	94	92	94	95	94	96	8
33	Sudha	25	83	84	80	83	83	78	83	86	77	78	82	80	84	80	7
34	Valli	26	93	92	90	87	90	92	95	92	89	91	92	94	93	90	8

35	Sumathi	24	83	82	79	83	82	80	81	79	78	96	98	100	100	95	9

MASTER CHART : GROUP B – BUPIVACAINE

S.No	NAME	AGE	WT	DURATION	VAPS				INITIAL BLOCK	2 SEG REG	COMPLICATIONS		
					2nd hr	3rd hr	4th hr	6th hr			Nausea Vomiting	Urinary retentio	
1	Syed Ali	20	52	85	6	X	X	X	T6	65	NIL	NIL	
2	Muthulakshmi	22	53	100	5	X	X	X	T6	70	NIL	NIL	
3	Rajeshwari	24	61	145	5	X	X	X	T5	100			
4	Sheik Fatima	25	64	133	5	X	X	X	T5	100	NIL	NIL	
5	Muthusundari	22	65	140	5	X	X	X	T5	115	NIL	NIL	
6	Anis Fatima	26	62	325	0	2	5	X	T4	240	NIL	NIL	
7	Subbuthai	23	58	215	0	2	5	X	T4	160	NIL	NIL	
8	Saradha	21	56	147	5	X	X	X	T5	95	NIL	NIL	
9	Andal	25	58	155	5	X	X	X	T5	100	NIL	NIL	
10	Shanthi	24	61	121	5	X	X	X	T5	75	NIL	NIL	
11	Pechiammal	25	63	165	2	5	X	X	T4	120	NIL	NIL	
12	Mahalakshmi	26	65	172	0	2	5	X	T4	125	NIL	NIL	
13	Syed ali	21	56	160	1	4	6	X	T4	120	NIL	NIL	

	Fatima												
14	Mari	22	64	228	0	2	5	X	T4	165	NIL	NIL	
15	Saraswathi	23	62	175	0	2	6	X	T4	125	NIL	NIL	
16	Gomathi	21	61	163	0	6	X	X	T4	120	NIL	NIL	
17	Priya	25	60	218	0	2	6	X	T4	155	NIL	NIL	
18	Ayisha begam	26	59	92	5	X	X	X	T6	55	NIL	NIL	
19	Roobini	25	62	160	2	6	X	X	T5	110	NIL	NIL	
20	Selvi	26	63	60	7	X	X	X	T6	40	NIL	NIL	
21	Mariammal	22	64	120	4	7	X	X	T5	75	NIL	NIL	
22	Sudali	23	65	120	5	X	X	X	T6	70	NIL	NIL	
23	Usha rani	20	65	144	0	5	7	X	T5	95	NIL	NIL	
24	Uma	22	62	150	0	4	6	X	T5	100	NIL	NIL	
25	Asha	21	61	360	0	2	4	6	T4	260	NIL	NIL	
26	Dhanam	24	62	200	0	4	7	X	T4	155	NIL	NIL	
27	Muthulakshmi	24	63	140	1	6	X	X	T5	85	NIL	NIL	
28	Saraswathi	25	60	215	1	4	6	X	T4	150	NIL	NIL	
29	Sophia	26	58	240	0	3	5	X	T4	180	NIL	NIL	
30	Prema	21	62	280	0	1	4	6	T4	220	NIL	NIL	
31	Banu	22	63	165	2	6	X	X	T6	110	NIL	NIL	
32	Amudharani	25	64	350	0	1	4	5	T4	285	NIL	NIL	
33	Maharasi	25	61	170	0	4	7	X	T6	115	NIL	NIL	
34	Rabia	26	60	215	0	3	6	X	T4	150	NIL	NIL	
35	Krithika	22	62	165	1	5	7	X	T5	115	NIL	NIL	

BUPIVACAINE HEMODYNAMIC PROFILE

S.no	NAME	AGE	MAP									PULSE RATE					
			5	10	15	20	30	45	60	90	120	5	10	15	20	30	
1	Syed Ali	20	66	72	72	70	78	82	81	91	87	78	86	84	85	91	
2	Muthulakshmi	22	80	86	84	85	90	90	88	94	96	92	90	87	86	84	
3	Rajeshwari	24	85	84	91	86	93	99	97	98	100	96	94	90	90	88	
4	Sheik Fatima	25	90	90	91	90	96	96	98	96	86	92	90	91	88	92	
5	Muthusundari	22	82	83	84	87	91	93	96	96	93	98	100	101	97	98	
6	Anis Fatima	26	99	93	93	95	94	98	99	96	96	98	92	88	84	84	
7	Subbuthai	23	87	86	92	89	92	85	86	87	80	84	86	87	84	80	
8	Saradha	21	82	83	81	84	83	92	88	83	82	94	96	92	90	86	
9	Andal	25	80	82	80	81	88	91	96	94	94	100	98	94	96	92	
10	Shanthi	24	84	88	93	90	82	78	79	80	79	79	82	84	80	82	
11	Pechiammal	25	80	85	83	84	84	93	95	84	82	90	91	92	90	86	
12	Mahalakshmi	26	80	84	80	86	88	91	94	98	95	78	84	86	82	85	

13	Syed ali Fatima	21	83	82	91	90	82	82	80	86	78	92	93	90	91	94	
14	Mari	22	83	87	81	82	82	83	83	80	83	78	84	85	86	84	
15	Saraswathi	23	90	90	89	90	93	92	86	93	90	93	84	86	87	8681	
16	Gomathi	21	84	85	86	87	82	83	78	83	83	87	88	89	90	90	
17	Priya	25	80	92	89	93	95	98	99	100	93	100	102	99	96	92	
18	Ayisha begam	26	93	95	88	82	84	78	82	81	83	86	84	80	78	84	
19	Roobini	25	94	88	84	82	92	96	95	96	93	90	91	92	88	84	
20	Selvi	26	83	88	92	92	92	89	91	94	93	72	75	76	74	78	
21	Mariammal	22	86	87	85	96	91	83	85	83	86	82	84	81	80	83	
22	Sudali	23	82	88	92	87	90	87	93	90	84	94	96	90	87	84	
23	Usha rani	20	79	81	83	82	80	83	85	80	82	83	84	86	87	86	
24	Uma	22	80	83	92	93	89	92	92	93	95	87	88	86	84	90	
25	Asha	21	83	89	93	91	95	101	99	99	98	94	95	96	91	88	
26	Dhanam	24	80	79	79	80	79	78	75	78	80	84	86	83	82	84	
27	Muthulakshmi	24	80	86	85	80	89	90	93	94	94	95	90	91	90	87	
28	Saraswathi	25	80	83	85	86	86	85	86	88	86	90	91	92	93	88	
29	Sophia	26	78	84	88	86	80	83	82	84	80	91	87	86	85	84	
30	Prema	21	84	87	88	85	86	80	84	84	92	104	106	100	102	108	
31	Banu	22	93	95	88	88	84	80	84	81	79	74	76	70	71	73	
3																	
32	Amutharani	25	70	72	77	80	76	89	88	86	86	83	86	90	90	96	
33	Maharasi	25	83	95	93	94	97	88	94	96	94	78	80	84	83	84	
34	Rabia	26	83	84	87	82	83	82	79	79	81	78	80	82	80	76	
35	Krithika	22	93	96	93	92	94	99	97	97	94	93	93	90	92	95	

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PROFORMA

The effect of intrathecal Clonidine on post-operative analgesia in pregnant patients undergoing lower segment caesarian section

Name : **Age:** **Ht:** **Wt:**

I.P.No: **Unit:** **Date:**

Obstetric score: **Gestational week:**

Type of surgery: Elective / Emergency **ASA status:**

Indication:

Drug history: **dose:** **duration:**

Investigations:

Hb : **Urine albumin :**

Blood Sugar : **Sugar :**

Urea : **deposits :**

Creatinine :

O/E

Anaemia : **Icterus :** **Edema :**

PR : **BP :**

Pre-med:

Anti-emetic prophylaxis

Inj. Ranitidine 50mg i.v.

Inj. Metoclopromide 10 mg i.v.

Pre-loading: I.V.Infusion of RL – 10ml / kg

Anaesthesia – SAB

Position : Rt lateral

Space : L3 – L4

Needle : 23G

Drug : B GROUP - 0.5% Bupivacaine 2ml

C GROUP - 0.5% Bupivacaine 2ml + 75 µg Clonidine

Parameters monitored

TIME Mins.	PR	MAP mmHg	SPO2 %	LEVEL OF INITIAL BLOCK	2 SEG REG Mins.	VAPS Hrs				TIME FOR SYSTEMIC ANALGESIC SUPPLEMENTATION Mins.
						2	3	4	6	
5										
10										
15										
20										
30										
45										
60										
90										
120										

Signature